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Varicella zoster virus vasculopathy: the expanding clinical spectrum and pathogenesis

Maria A. Nagel*, Dallas Jones, and Ann Wyborny

Department of Neurology, University of Colorado School of Medicine, Aurora, CO 80045, USA

Abstract

Varicella zoster virus (VZV) is a ubiquitous, human alphaherpesvirus that produces varicella on primary infection then becomes latent in ganglionic neurons along the entire neuraxis. In elderly and immunocompromised individuals, VZV reactivates and travels along nerve fibers peripherally resulting in zoster. However, VZV can also spread centrally and infect cerebral and extracranial arteries (VZV vasculopathy) to produce transient ischemic attacks, stroke, aneurysm, sinus thrombosis and giant cell arteritis, as well as granulomatous aortitis. The mechanisms of virus-induced pathological vascular remodeling are not fully elucidated; however, recent studies suggest that inflammation and dysregulation of programmed death ligand-1 play a significant role.

Graphical Abstract

Keywords

varicella zoster virus; vasculopathy; inflammation; stroke; giant cell arteritis; aortitis

*Corresponding author: Maria A. Nagel, M.D., Department of Neurology, University of Colorado School of Medicine, Aurora, Co, USA, maria.nagel@ucdenver.edu, telephone: 303-724-4326.

Statement of interest

The authors declare no conflict of interest.

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1. Introduction

Varicella zoster virus (VZV) is an exclusively human neurotropic alphaherpesvirus that infects more than 95% of the U.S. population. Primary infection typically results in varicella (chickenpox), followed by establishment of virus latency in neurons of the cranial nerve, dorsal root and autonomic ganglia along the entire neuraxis, as well as of the adrenal glands (Badani et al., 2016). With a decline in VZV-specific cell-mediated immunity in elderly and immunocompromised individuals, defects in innate immunity (particularly NK cell defects; Levy et al., 2003; Orange, 2013) or the presence of anti-cytokine antibodies (Burbello et al., 2010; Chi et al., 2013), virus reactivates from one of more ganglia, travels peripherally to skin and produces herpes zoster (shingles) in the corresponding dermatome(s). Zoster is frequently complicated by postherpetic neuralgia, which is the leading cause of pain-related suicide in the elderly (Schmader et al., 1998).

During reactivation, VZV can also travel centrally to produce other neurological and ocular diseases with or without associated zoster rash. One such disease is VZV vasculopathy produced by direct VZV infection of arteries that is associated with inflammation and clinical symptoms and signs. VZV vasculopathy was first described in 1896 (Baudouin and Lantuejoul, 1919) and included cases of varicella or zoster that was temporally associated with stroke, particularly when zoster occurred in the ophthalmic division of the trigeminal nerve (herpes zoster ophthalmicus with contralateral hemiparesis). Subsequently, affected cerebral arteries from patients with VZV vasculopathy were examined postmortem and found to have VZV DNA following DNA extraction from affected arteries and PCR for viral DNA, VZV antigen by immunohistochemical analyses and herpesvirus particles by electron microscopy (Fukumoto et al., 1986; Gilden et al., 1996) demonstrating that VZV vasculopathy was due to productive virus infection of arteries. Over the past few decades, the clinical spectrum of VZV vasculopathy has expanded to include extracranial vasculopathy presenting as giant cell arteritis, the most common systemic vasculitis in the elderly, and granulomatous aortitis. Herein, we will discuss these varied clinical presentations, as well as the pathogenesis of VZV infection of arteries and persistent inflammation contributing to pathological vascular remodeling.

2. Epidemiology

VZV infection as a cause of stroke is supported by the clear demonstration that *zoster is a stroke risk factor* in multiple epidemiological studies from Taiwan, Denmark, the U.K., Sweden and the U.S. Two studies using the Taiwan National Health Research Institute records revealed a 30% increased risk of stroke within 1 year following zoster (Kang et al., 2009) and a 4.5-fold increased risk if zoster occurred in the ophthalmic division of the trigeminal nerve (Lin et al., 2010). A study using records from the Danish National Registry indicated that after zoster, there was a 126% increased risk of stroke within 2 weeks, 17% increased risk from 2 weeks to 1 year and 5% increased risk after the first year (Sreenivisan et al., 2013). A study from the UK Health Improvement Network general practice database showed that the risk for transient ischemic attacks (TIAs) and myocardial infarctions (MIs) were increased by 1.15- and 1.10-fold, respectively, in all patients with zoster; however, in patients under 40 years of age with zoster, the risk for stroke, TIAs and MIs was

significantly higher (1.74-, 2.42- and 1.49-fold, respectively) (Breuer et al., 2014). A study from the U.K. Clinical Practice Research Datalink showed a decreasing risk of stroke over time after zoster in all dermatomes, with a statistically significant age-adjusted incidence at 1–4 weeks after zoster (1.63), 5–12 weeks after zoster (1.42), and 13–26 weeks after zoster (1.23), but no increase at later times (Langan et al., 2014). In patients with ophthalmic-distribution zoster, the risk of stroke was increased 3-fold at 5 to 12 weeks after zoster. Finally, among 55% of zoster patients who received oral antiviral therapy, the stroke risk was reduced compared to that in untreated zoster patients, indicating the value of antiviral treatment in reducing stroke incidence after zoster.

Recently, a register-based cohort study in Sweden showed a 1.34-fold increased risk of stroke within 1 year after zoster in all age groups (Sundström et al., 2015). Like the U.K. study, in patients 39 years and younger, the risk of stroke was increased 10.3-fold within 1 year after zoster. Another U.K. study showed that the risk of stroke and MI increased 2.4- and 1.7-fold, respectively, within 2 weeks after zoster (Minassian et al., 2015). Finally, in the first U.S. population-based study, the risk of stroke within 3 months of zoster was increased 1.53-fold (Yawn et al., 2015). While stroke in the pediatric population is rare, approximately one-third of arterial ischemic stroke is associated with varicella (Askalan et al., 2001) and 44% of transient cerebral arteriopathy is preceded by varicella (Braun et al., 2009). Overall, these combined studies show that varicella and zoster are risk factors for stroke, particularly in individuals who develop zoster under 40 years of age, consistent with central spread of VZV to arteries in addition to peripheral spread to skin; furthermore, antiviral therapy may decrease this stroke risk and should be considered in all cases of zoster.

3. Clinical features, laboratory abnormalities, diagnosis and treatment of VZV vasculopathy

Historically, VZV vasculopathy was initially characterized as involving intracranial arteries and presented as transient ischemic attacks (TIAs) and ischemic or hemorrhagic strokes. In 30 patients with virologically-confirmed VZV vasculopathy (Nagel et al., 2008), rash was present in 63%, cerebrospinal (CSF) pleocytosis was detected in 67% and the average time from rash to neurological symptoms and signs was 4.1 months. Brain MRI and CT abnormalities were present in 97%, typically seen as enhancing lesions at grey-white matter junctions. Of 23 patients analyzed by angiography, 70% had abnormalities predominantly in both large and small arteries (50%), small arteries exclusively (37%), and large arteries exclusively (13%). Due to the protracted nature of disease, VZV DNA was detected in only 30% of CSF samples whereas anti-VZV IgG antibody was found in 93% of CSF samples, including a reduced serum/CSF ratio of anti-VZV IgG that confirmed intrathecal synthesis of anti-VZV IgG (Nagel et al., 2007, 2008). While both PCR and detection of antibody to VZV in CSF are highly specific, detection of anti-VZV IgG antibody in CSF is the more reliable test to diagnose VZV vasculopathy (Nagel et al., 2007). Overall, a positive PCR for VZV DNA in CSF can be diagnostic, but a negative PCR does not exclude the diagnosis; only negative results in both VZV PCR and anti-VZV IgG antibody testing in CSF excludes the diagnosis of VZV vasculopathy. Unfortunately, the diagnosis of VZV vasculopathy is often missed, and hence antiviral treatment not administered, due to the lengthy time

between the occurrence of rash to stroke, the absence of rash or the absence of a pleocytosis and VZV DNA in CSF.

In children, post-varicella stroke is usually monophasic (Lanthier et al., 2005), typically presenting as an acute hemiparesis at, on average, 4 months after varicella (Cicone et al., 2010; Miravet et al., 2007). Recently, the live attenuated varicella vaccine strain was shown to cause VZV vasculopathy in an immunodeficient child (Sabry et al., 2014), indicating the need for caution in vaccinating potentially immunocompromised children.

Less commonly, VZV vasculopathy can present as aneurysms with subarachnoid hemorrhage. A classic case describes a 41-year-old woman with systemic lupus erythematosus treated with methotrexate (Liberman et al., 2014), who developed zoster in multiple dermatomes and severe headache; 2 months later, subsequent 4-vessel digital subtraction angiography revealed 9 anterior circulation aneurysms. Treatment with intravenous acyclovir resulted in resolution of symptoms, reduction in the size of most aneurysms and complete resolution of the 2 largest aneurysms. Rarely, VZV vasculopathy may also present as acute venous sinus thrombosis (Siddiqi et al., 2012). In a classic case, a 30-year-old man developed varicella followed 1 week later by neurological deficits; MR venography demonstrated a transverse and sigmoid sinus thrombosis. In 2 other cases, patients presented with zoster followed by seizures and extensive cerebral venous sinus thrombosis on neuroimaging.

VZV vasculopathy should be suspected in individuals, particularly if immunocompromised, who have had a stroke or aneurysm with: (1) a recent history of varicella or zoster, (2) recurrence of unclear cause with or without rash, or (3) unclear etiology and absence of stroke risk factors. The best test for diagnosis in these suspected cases is a lumbar puncture and examination of CSF for the presence of anti-VZV antibodies and VZV DNA as noted above. Patients with VZV vasculopathy are treated with 10–15 mg/kg intravenous acyclovir for 14 days based upon Level 2 class of evidence (systemic review of cohort studies or individual cohort studies) extrapolated from treatment studies of herpes simplex virus central nervous system disease (reviewed in Wilck et al., 2013), as well as expert opinions and case series without controls of VZV vasculopathy (Nagel et al., 2008). For recurrent disease, a second course may be required, particularly in immunocompromised patients, followed by oral antivirals for several months. The dose of acyclovir is adjusted per creatinine clearance and patients advised to stay hydrated due to potential nephrotoxicity. Since histological specimens often demonstrate arterial inflammation, we concurrently administer prednisone, 1 mg/kg from days 1–5 of the 14 day acyclovir course without the need for a subsequent steroid taper.

4. Giant cell arteritis

In the past few years, multiple studies emerged that indicated that VZV vasculopathy can also affect the extracranial circulation including temporal arteries (TAs) from patients with giant cell arteritis (GCA). GCA is the most common systemic vasculitis in the elderly and is characterized by a constellation of symptoms including severe headache, scalp tenderness and vision loss, as well as a history of jaw claudication, polymyalgia rheumatica, fever, night

sweats, weight loss, fatigue and elevated inflammatory markers (erythrocyte sedimentation rate and C-reactive protein). Diagnosis of biopsy-positive GCA (GCA-positive) is made by the presence of transmural inflammation, medial smooth muscle cell damage, and multinucleated giant or epithelioid cells in non-contiguous skip lesions of temporal artery (TA biopsies). In many clinically suspect cases, TA biopsy may be pathologically negative (GCA-negative) and decision to treat is based upon clinical presentation. Since vision loss frequently occurs, patients are immediately treated with corticosteroids, with 50% of patients relapsing after discontinuation of therapy or progressing to stroke and vision loss despite therapy. The cause of GCA was not clear but activation of vascular dendritic cells in the artery wall by an unknown antigen in the adventitia was proposed as an early step in disease progression (Ma-Krupa et al., 2004).

Analyses to test for the possible role of VZV infection in GCA were motivated by the virtually identical pathological changes seen in patients with intracerebral VZV vasculopathy and GCA, as well as multiple case reports and series demonstrating an overlap between features of GCA and VZV vasculopathy (Salazar et al., 2011; Mathias et al., 2013; Nagel et al., 2013a, 2013b). In both conditions, pathology is characterized by granulomatous arteritis, in which inflammation, often transmural, is seen together with necrosis, usually in the arterial media; multinucleated giant cells, epithelioid macrophages or both are also present. An initial study of GCA-negative TAs from 24 patients with clinically-suspected GCA detected VZV antigen immunohistochemically in 5/24 (21%) of TAs primarily in the arterial adventitia where VZV is initially deposited following reactivation; no HSV-1 antigen was seen. Thirteen normal TAs did not contain VZV or HSV-1 antigen (Nagel et al., 2013c). A subsequent case revealed VZV antigen in skip areas of a GCA-negative TA; pathological analysis of sections adjacent to those containing viral antigen showed inflammation involving the arterial media and abundant multinucleated giant cells characteristic of GCA (Nagel et al., 2013b), leading to a change in diagnosis from biopsy-negative to biopsy-positive GCA. These initial studies provided support for the notion that VZV infection triggers the inflammatory cascade characteristic of GCA.

A more extensive study of GCA biopsy-positive TAs (50 sections/TA) revealed VZV antigen in 61/82 (74%) these TAs compared with 1/13 (8%) normal TAs ($p<0.0001$) (Gilden et al., 2015). Most GCA-positive TAs contained viral antigen in skip areas and mostly in the arterial adventitia followed by the media and intima. Despite formalin fixation, VZV DNA was readily detected in 18/45 (40%) GCA-positive/VZV antigen-positive TAs and in 1 VZV antigen-positive normal TA. Electron microscopy also demonstrated VZ virions in the same region of a GCA-positive TA that contained viral antigen on an adjacent section. GCA pathology in sections adjacent to those containing VZV was seen in 89% of GCA-positive TAs, but in none of 18 adjacent sections from normal TA. Overall, most GCA-positive TAs contained VZV in skip areas that correlated with adjacent GCA pathology, strongly suggesting that VZV triggers GCA immunopathology.

A similar study of GCA-negative TAs showed VZV antigen in 45/70 (64%) compared with 11/49 (22%) normal TAs ($p<.001$) (Nagel et al., 2015a), and extension of the study above (Gilden et al., 2015) revealed VZV antigen in 68/93 (73%) of GCA-positive TAs compared with 11/49 (22%) normal TAs ($p<.001$). Compared to the prevalence in normal TAs, VZV

antigen was more likely to be present in both GCA-negative TAs ($p<.001$) and GCA-positive TAs ($p<.001$). Of 44 GCA-negative patients whose TAs contained VZV antigen, 16 (36%) showed adventitial inflammation adjacent to viral antigen; no inflammation was seen in normal TAs. Together, our data suggest that the prevalence of VZV in TAs of patients with clinically-suspected GCA is similar, regardless of whether biopsy is negative or positive pathologically, and that GCA-negative TAs may represent early VZV vasculopathy where inflammation is initially restricted to adventitia - thus further expanding the spectrum of VZV vasculopathy to extracranial arteries.

Finally, a cumulative study encompassing previous studies on the frequency of VZV in GCA-positive, GCA-negative and normal TAs (Gilden et al., 2016a) detected VZV antigen in 73/104 (70%) GCA-positive TAs and in 58/100 (58%) GCA-negative TAs; the presence of VZV antigen in these 2 groups was statistically significant ($p<0.0001$) compared to 11/61 (18%) normal TAs that contained VZV antigen. VZV DNA was detected by PCR in many VZV antigen-positive sections. Adventitial inflammation was seen adjacent to viral antigen in 26 (52%) of 58 GCA-negative subjects whose TAs contained VZV antigen and no inflammation was seen in normal TAs containing VZV antigen, most likely reflecting subclinical reactivation in some people over age 50. Overall, the greater frequency of VZV in the adventitia than in media and intima in all groups (86% of GCA-positive subjects and 95% of GCA-negative subjects) most likely reflects transaxonal transport of virus along afferent nerve fibers that innervate the TA after reactivation from ganglia.

Taking together the significant association of VZV antigen in TAs of patients with GCA-negative and GCA-positive TAs compared to normal TAs and the same pathologies and vascular presentations of giant cell arteritis and VZV vasculopathy, VZV appears to trigger the immunopathology of a significant subset of GCA and antiviral treatment is likely to confer benefit in addition to corticosteroids. We currently treat GCA with prednisone, 1 mg/kg, along with valacyclovir, 1 g three times daily (Level 5 class of evidence: expert opinion without explicitly critical appraisal, or based on physiology, bench research, or “first principles”). If the patient improves after 4–6 weeks, we recommend tapering prednisone, while continuing administration of antiviral agents for another 4–6 weeks. Long-term antiviral drugs are far less risky than long-term corticosteroids. Furthermore, if during a prednisone taper, patients’ symptoms recur or worsen, along with increases in ESR or CRP, oral antivirals should be added rather than increasing the prednisone dose. In our experience, antiviral treatment has successfully normalized symptoms and inflammatory markers. However, rigorous prospective studies are needed to determine whether oral antiviral agents and corticosteroids are as effective as intravenous acyclovir and corticosteroids, as well as appropriate dosage and duration of treatment.

5. Granulomatous aortitis

Granulomatous aortitis is a rare disease in which pathology of the aorta is the same as that seen in virus-infected arteries from intracranial VZV vasculopathy and extracranial giant cell arteritis. Examination of 11 human aortas from patients with granulomatous aortitis using 3 different anti-VZV antibodies revealed VZV antigen in all 11 (100%) and 5/18 (28%) of normal aortas controls (Gilden et al., 2016b). The presence of VZV antigen in

granulomatous aortitis was highly significant ($P = .0001$) as compared to control aortas, in which VZV antigen was never associated with pathology, indicating subclinical reactivation. VZV DNA was found in most aortas containing VZV antigen. The frequent clinical, radiological, and pathological aortic involvement in patients with giant cell arteritis correlates with the significant detection of VZV in granulomatous aortitis. Similar to VZV infection of temporal and cerebral arteries, VZV can reactivate from thoracic dorsal root ganglia, as well as thoracic sympathetic ganglia (Nagel et al., 2014a), to infect the aortic adventitia where these nerve fibers can terminate.

6. VZV in normal human temporal arteries and intracerebral arteries

Analysis of >250 TAs from patients who were GCA-positive or –negative and control TAs obtained postmortem from subjects >50 years without stroke or GCA, revealed the presence of VZV in 11/49 (22%) of control TAs (Nagel et al., 2015a). The detection of late VZV proteins (VZV glycoprotein E) without any associated inflammation most likely reflects subclinical reactivation in elderly patients without vasculopathy. Indeed, 7 of the 11 control TAs that contained VZV antigen were from subjects at high risk for reactivation due to cancer, diabetes, corticosteroid use or alcohol abuse.

Our studies of intracerebral VZV vasculopathy included examination of 63 cerebral arteries from 45 normal subjects (Nagel et al., 2013d). No VZV antigen was found when one formalin-fixed, paraffin-embedded (FFPE) section was analyzed from each sample, and no VZV DNA was detected by PCR from 20 mg of total DNA from each sample. Two subsequent studies examined cerebral arteries from subjects at high risk for VZV reactivation. Analysis of cerebral arteries from 4 diabetic subjects, who are at a higher risk for zoster and stroke (Heymann et al., 2008), revealed VZV DNA (3,740 copies per mg total DNA) in the artery of 1 subject; further analysis of 20 corresponding FFPE sections of this VZV DNA-positive artery revealed viral antigen in non-contiguous regions (skip lesions) of adventitia, with rare inflammatory cells immediately adjacent to viral antigen (Nagel et al., 2012). In another study, FFPE sections from 55 cerebral arteries from 18 subjects with comorbidities that may increase VZV reactivation were obtained; immunohistochemical analysis of 10–12 sections from HIV-negative arteries and 2 sections from HIV-positive arteries detected VZV antigen in 44% arteries and 78% subjects with a history of alcohol abuse, tricyclic antidepressant intoxication, cocaine abuse, multiple myeloma, HIV and age >70 years (Nagel et al., 2014b). Of the 5 HIV+ subjects, 4 (80%) showed VZV antigen in arteries.

Additional studies are needed to determine the significance of the presence of VZV in some normal arteries, particularly temporal and intracerebral arteries obtained at autopsy from subjects in high-risk groups. To date, the presence of VZV antigen in normal temporal and intracerebral arteries, including arteries from subjects in high-risk groups, has not been shown to be associated with inflammation or the pathology of GCA or intracerebral vasculopathy. This most likely supports the notion that VZV in the artery alone is not sufficient to trigger a vasculopathy, and host variability that may predispose or attenuate the damaging inflammatory response plays a significant role in disease progression and remains to be explored.

7. Pathogenesis

Because no animal model exists for stroke caused by VZV vasculopathy, pathogenesis studies have been restricted to arteries from subjects with VZV vasculopathy and primary human cerebrovascular cells infected with VZV. Immunohistochemical analysis of cerebral and temporal arteries from 3 patients with virologically-confirmed VZV vasculopathy revealed VZV antigen in the outermost adventitial layer of the artery early in infection and in the media and intima later in the course of disease, consistent with transaxonal spread of reactivated VZV to the arterial adventitia followed by transmural spread of virus (Nagel et al., 2011). VZV-infected arteries contained: (1) a disrupted internal elastic lamina; (2) a thickened intima composed of myofibroblasts expressing alpha-smooth muscle actin, potentially contributing to luminal narrowing/occlusion and ischemic stroke; and (3) a paucity of medial smooth muscle cells leading to loss of vesselwall integrity (Nagel et al., 2011). The expression of myosin in some of the myofibroblasts indicate that these cells may have originated from the media. VZV-infected arteries contained CD4+ and CD8+ T cells, CD68+ macrophages and rare B cells expressing CD20 distributed in the adventitia and intima, but not the media (Nagel et al., 2013e). Arteries from early VZV vasculopathy contained abundant neutrophils in the adventitia, which were absent in late VZV vasculopathy. Inflammatory cells were absent in control arteries.

The presence of neutrophils in the arterial adventitia in early VZV vasculopathy is consistent with their presence in the CSF of patients with neurological disease due to VZV (Amlie-Lefond et al., 1995; Devinsky et al., 1991; Gilden et al., 1994, 1996; Haug et al., 2010; Stevens et al., 1975). Although the mechanisms of vascular remodeling triggered by VZV are unknown, neutrophils may play a role since they produce reactive oxygen species in response to infection, which may mediate smooth muscle cell proliferation and migration (Hartney et al., 2011; Weber et al., 2004) and induce apoptosis and loss of vascular smooth muscle cells (Hsieh et al., 2001; Li et al., 2003). Neutrophils also secrete elastase and matrix metalloproteinases (MMPs; together with activated matrix metalloproteinases directly secreted by VZV infected vascular cells (Nagel et al., 2015b) – these enzymes can lead to extracellular matrix breakdown, weakening of the vessel wall and aneurysm formation (Ferry et al., 1997; Itoh and Nagase, 1995; Okada and Nakanishi, 1989). Finally, a thickened intima was associated with inflammation in vaso vasorum vessels in early VZV vasculopathy, consistent with the notion that inflammatory cells secrete soluble factors that contribute to pathological vascular wall remodeling (Frid et al., 2006; Stenmark et al., 2012).

In an attempt to identify biomarkers for VZV vasculopathy, CSF from 30 patients with virologically-confirmed VZV vasculopathy were analyzed for levels of proinflammatory cytokines and MMPs (Jones et al., 2016a). As positive controls for CNS inflammatory disease, CSF from 30 patients with multiple sclerosis (MS) was studied, along with CSF from 20 healthy individuals to serve as negative controls. Compared to CSF of both MS and healthy controls, CSF from VZV vasculopathy patients had significant elevations in interleukin (IL)-8, IL-6, and MMP-2. These results might help explain the abundance of neutrophils and macrophages observed in VZV vasculopathy patients, since IL-8 is a chemoattractant for neutrophils and IL-6 promotes macrophage differentiation. Increased

levels of IL-8 and IL-6 along with MMP-2 could contribute to the inflammation and vascular wall damage that are hallmarks of VZV vasculopathy.

A recent study to identify mechanisms contributing to the persistence of inflammatory cells in VZV-infected arteries months after disease onset focused on the dysregulated expression of programmed death ligand-1 (PD-L1) during VZV infection of primary vascular cells *in vitro* (Jones et al., 2016b). PD-L1 is a 40-kDa type 1 transmembrane protein in the B7 immunoglobulin family that can be expressed on virtually all nucleated cells. It acts to suppress the immune system through interaction with its receptor, programmed cell death protein 1 (PD-1), which is expressed specifically on activated T cells, B cells and macrophages. VZV infection of various vascular cells *in vitro* lead to downregulation of PD-L1 expression, which only occurred after the VZV-mediated downregulation of major histocompatibility complex-I (MHC-I). Downregulation of PD-L1 could promote persistent inflammation in the infected arteries and explain how immune cells persist up to 10 months after diagnosis, while the initial downregulation of MHC-I could prevent viral clearance. These studies also identified a VZV-mediated downregulation of MHC-I in uninfected bystander cells that would further inhibit viral clearance in the infected arteries.

8. Conclusions

VZV vasculopathy is a potentially treatable cause of vascular disease and should be suspected in patients with zoster or varicella followed by transient ischemic attacks, ischemic and hemorrhagic stroke, aneurysm, sinus thrombosis and giant cell arteritis, as well as granulomatous aortitis. It is important to recognize that the absence of rash, a CSF pleocytosis or VZV DNA in CSF does not exclude the diagnosis, particularly in immunosuppressed individuals. Characteristic features include imaging and angiographic abnormalities involving both large and small vessels. The best test for diagnosis is detection of anti-VZV IgG in the CSF. Treatment consists of intravenous acyclovir, as discussed in the VZV vasculopathy and giant cell arteritis sections. While the mechanisms of VZV vasculopathy have not been fully elucidated, histological and immunohistochemical studies of VZV infected arteries, analysis of CSF from VZV vasculopathy patients for cytokines and MMPs and analysis of VZV-infected primary human vascular cells for MMPs, PD-L1 and MHC-I provide a potential model. Specifically, upon VZV reactivation from sensory and/or autonomic ganglia, virus travels along nerve fibers that terminate in the outermost adventitial layer of the artery where virus-infected adventitial fibroblasts elicit a robust inflammatory response involving neutrophils early in disease, and T cells and macrophages throughout the entire course of disease. VZV-infected cells, neutrophils and other infiltrating immune cells produce activated MMPs which degrade the extracellular matrix potentially leading to weakening of the vessel wall, aneurysm formation and rupture. Soluble factors secreted by inflammatory cells further contribute to vascular smooth muscle death and accumulation of myofibroblasts in the thickened intima potentially leading to occlusion of blood flow and ischemic stroke. Finally, downregulation of PD-L1 in VZV-infected vascular cells contributes to the persistence of inflammatory cells and downregulation of MHC-I may prevent effective viral antigen presentation to immune cells.

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Abbreviations

GCA	giant cell arteritis
IL	interleukin
MHC-1	major histocompatibility complex class I
MMP	matrix metalloproteinase
PD-L1	programmed death ligand-1
TA	temporal artery
VZV	varicella zoster virus

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Highlights

- VZV vasculopathy produces stroke, giant cell arteritis and granulomatous aortitis.
- VZV vasculopathy is due to productive virus infection of arteries.
- VZV-induced arterial inflammation contributes to pathological vascular remodeling.
- Downregulation of programmed death ligand-1 contributes to persistent vasculitis.
- Downregulation of MHC-I leads to ineffective virus clearance.